NEUROCOGNITIVE SIDE EFFECTS OF HIGH DOSE METHOTREXATE AND CRANIAL RADIOTHERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS ON BFM 86 PROTOCOL TREATMENT

This dissertation is submitted to

The Tamilnadu Dr MGR Medical University, Chennai in partial fulfillment of the regulations for D.M.(Medical Oncology) Degree Examination of August 2010

CANCER INSTITUTE (W.I.A)

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CERTIFICATE

This is to certify that this dissertation on " **NEUROCOGNITIVE SIDE EFFECTS OF HIGH DOSE METHOTREXATE AND CRANIAL RADIOTHERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS ON BFM 86 PROTOCOL TREATMENT" is a bonafide work done by Dr Arun Seshachalam, in the department of Medical oncology, College of Oncological sciences, Adyar, Chennai, under my overall supervision and guidance, to my satisfaction.**

Chennai
25/05/2010

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ACKNOWLEDGEMENT

Words are inadequate to express my gratitude, towards each and everyone, who has been a guiding force and inspiration for me in making this dissertation, without whom all this effort would have never seen the light of the day.

I humbly wish to place on record my deep sense of gratitude to **Dr T G Sagar, MD , DM**, Director Cancer Institute(WIA) , Adyar , Chennai , Professor and Head , Chairman , Division of Medical Oncology, who with his profound knowledge and experience gave me constant support, encouragement and guidance during the entire part of this study.

I extend my gratitude to **Dr Ganapathy Ramanan MD, DM** who has been a constant inspiration to young medical Oncologists through all his charismatic teaching skills.

I express my sincere thanks to **Dr Rejiv Rajendranath MD,DM,DNB**, Associate Professor , Department of Medical Oncology for all his guidance and meticulous correction of my dissertation work.

My heartfelt thanks to **Dr R Swaminathan MSc , PhD** , who patiently helped me with statistical analysis.

I also owe my sincere thanks to **Dr V Srinivasan MD** for being a constant source of encouragement. I thank all my teachers within and outside the Institute, without whom I am not , what I am today.

I am extremely grateful to my fellow colleagues for all constructive suggestions.

I also extend my respect and gratitude to my parents, specially thank my wife and my daughter , who have made my life worthwhile.

Finally I thank **Dr Vidhubala MSc , PhD and Mr. Sundaramoorthy MSc** , Department of Psycho-Oncology without whom this study would not have been possible.

Last but not the least; I would like to thank all the patients who participated in the study.

My acknowledgement will be incomplete if I do not mention about **Dr Krishnamurthy** , advisor and **Dr V Shanta** Executive Chairman of Cancer Institute (WIA), whom I have always admired and drawn inspiration from, and whose blessings I will seek throughout my endeavor, in this field of Medical Oncology.

CONTENTS

Introduction

Cancer in children is rare: only 1 or 2 children per 10,000 are diagnosed with it each year. Nevertheless, it is the leading cause of death by disease in children under 5 years old. In the USA, 5-year survival for all type of childhood cancers increased from 51% in 1973 to79% in 1997[1] Incidence of childhood cancer in India is 9 per million [2]. Advances in the early diagnosis and treatment of pediatric cancers have led to dramatic increases in survival rates, especially for diseases such as leukemia. Several decades ago, a diagnosis of acute lymphoblastic leukemia (ALL) was almost always fatal, but a child diagnosed with it today has about a 90% chance of long-term survival (>5 years). 5 year survival rates for childhood cancers have reached 55% in our institute[3]. The use of prophylactic cranial radiotherapy (CRT), High dose methotrexate and multidrug regimens are largely responsible for this success [4]. The therapy responsible for this survival can also produce adverse neurocognitive side effects. In an effort to reduce the side effects most of the international protocols has avoided cranial radiotherapy in low risk ALL cases and reduced the dose of presymptomatic cranial radiotherapy in others. As an alternative to cranial radiotherapy high dose methotrexate is also incorporated in many of the protocols. But still a small subset of ALL cases end up receiving both cranial radiotherapy and high dose methotrexate [5-9]. There is paucity of literature regarding the neurocognitive side effects of combined cranial radiotherapy [CRT] & High dose methotrexate.

Aim of the study

To prospectively study the immediate Neurocognitive side effects of combined presymptomatic cranial radiotherapy and High dose methotrexate on Acute lymphoblastic leukemia patients during BFM 86 protocol treatment.

REVIEW OF LITERATURE

For children diagnosed with cancer in the early 1970's, the probabilities were approximately the same as to whether they would be cured or succumb to their illness. For children diagnosed in the early 1990's, the overall prognosis for survival had increased to 75% with some types of cancer exceeding 80% cure rates [10]. With improvement in survival, clinicians became more aware of late occurring adverse effects of treatment for childhood cancer. Neurocognitive late effects, defined by problems with thinking, learning, and remembering, have become an expanding area of scientific interest, especially for childhood cancer.

Although estimates vary according to patient diagnosis and age, aggressiveness of therapy, and length of follow-up, most researchers would agree that the incidence of neurocognitive late effects is unacceptably high. Despite recent attempts to modify therapy to reduce morbidity while maintaining high cure rates, problems in neurocognitive functioning remain to be experienced by a large majority of survivors. Efforts to eliminate neurocognitive late effects have been hampered by a deficient understanding of the biological and developmental mechanisms responsible, as well as a lack of clinical trials directed at treating the deficits associated with this neurocognitive syndrome.

Conceptual Model of Factors influencing neurocognitive functioning [11].

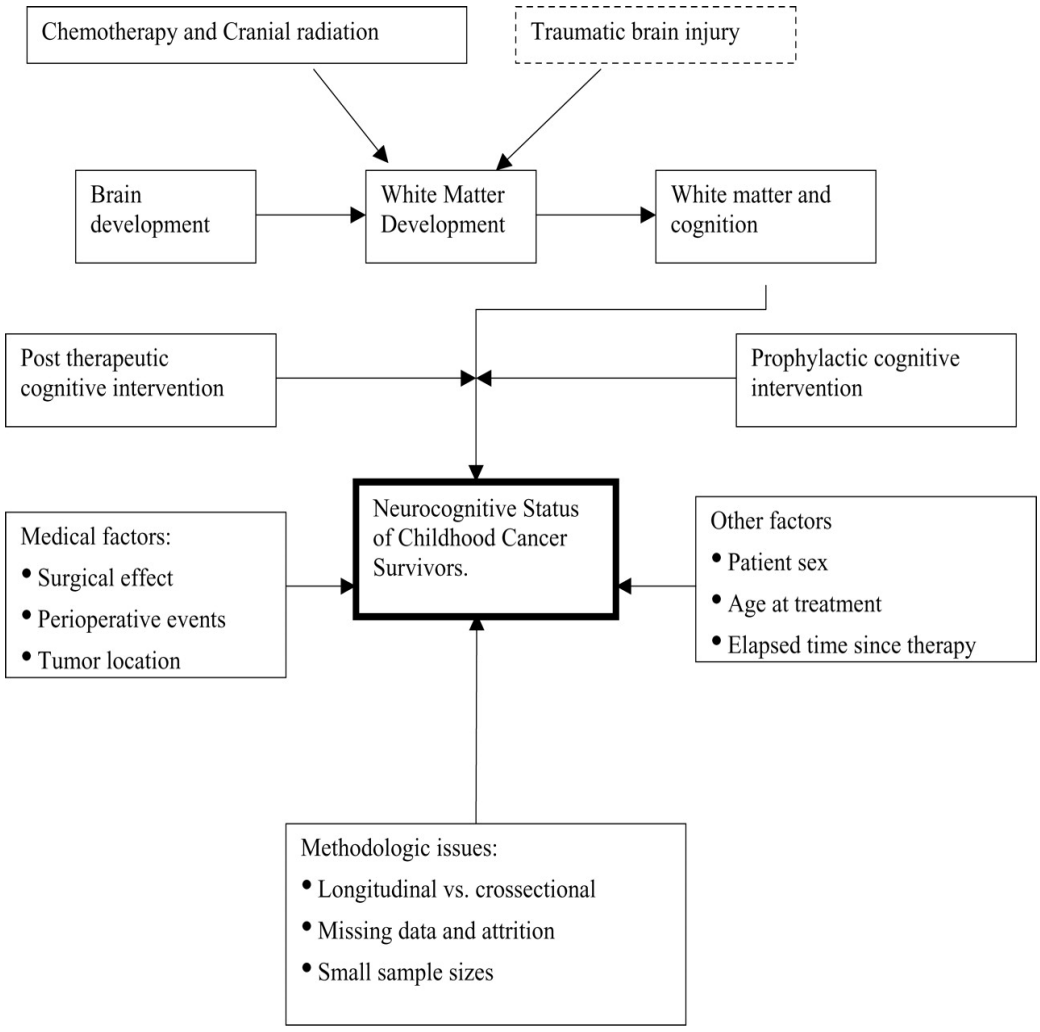


Figure 1. Conceptual Model of Factors Influencing neurocognitive functioning.

This conceptual model encompasses recognizes the influence of premorbid factors (e.g., genetic endowment, gender, and age) at the time of central nervous system damage, the potential for both neurobiological and environmental compensatory systems, the resulting core symptoms and secondary symptoms of the neurocognitive syndrome, and the potential impact of pharmacological and behavioral interventions to modify the expression of the symptoms. In preparation for more specific discussion of these factors, a brief review of pediatric ALL and associated sources of CNS are as follows

Acute Lymphoblastic Leukemia

Medical Background

Leukemia is the most common malignant neoplasm in childhood, accounting for about 41% of all malignancies that occur in children younger than 15 years of age. In the year 2000, approximately 3,600 children were diagnosed with leukemia in the United States, for an annual incidence of 4.1 new cases per 1, 00, 000 children younger than 15 years of age. Acute Lymphoblastic Leukemia (ALL) accounts for about 77% of cases of childhood leukemia, Acute Myeloid Leukemia (AML) for about 1%, Chronic Myeloid Leukemia (CML) for 2-3% and Juvenile Chronic Myeloid Leukemia (JCML) for 1-2%. The remaining 7-9% of cases includes a variety of acute and chronic leukemia's that do not fit classic definitions of ALL, AML, CML or JCML [12, 13].

The National Cancer Registry report reveals that the number of children diagnosed with cancer in the year 2005-2006 in Mumbai is 48,199, Bangalore 23,435 cases, Chennai 23,283 cases and Thiruvanandapuram 24,844, respectively. During the same period, in Chennai 1053 cases were diagnosed with leukemia of which 41.5% are children aged below 15 years. Of the total leukemia cancers 37.2% constituted acute lymphoblastic leukemia [14].

Although genetic, environmental, viral, and immunodeficiency factors have been implicated in the pathogenesis of ALL, the precise causes of most cases of ALL remain largely unknown. Presenting symptoms include fever, fatigue, pallor, anorexia, bone pain and bruising. The duration of treatment varies from 30 to 36 months which includes CNS directed therapy in the form of cranial radiotherapy and High dose methotrexate. A better prognosis is associated with female gender, age at diagnosis between 2 and 10 years, a lower white blood cell count, and an earlier positive response to treatment. Treatment can be divided into 4 phases: remission induction, CNS preventive therapy, consolidation, and maintenance. Induction therapy is the initial phase of treatment and is designed to place the patient in remission. More than 90 percent of children and adolescents with ALL enter CR at the end of induction therapy regardless of their initial risk grouping. Consolidation or intensification therapy is the second phase of ALL treatment and is initiated soon after attainment of CR. Ongoing treatment is required because small numbers of leukemic lymphoblasts remain in the bone marrow despite histologic evidence of CR after induction therapy. In such cases, relapse occurs quickly if therapy is not continued. The goal of post-induction chemotherapy is to prevent leukemic regrowth, reduce residual tumor burden, and prevent the

emergence of drug-resistance in the remaining leukemic cells. After completion of the consolidation or intensification phase of therapy, patients often receive a less intensive continuation regimen using daily oral 6-mercaptopurine (6-MP) and weekly methotrexate with periodic intrathecal therapy. Maintenance therapy is required for a prolonged period because of the presence of undetectable levels of leukemia that, nevertheless, have the capacity to be fatal [15]. After the completion of treatment, approximately 20% of those children who will eventually relapse will do so in the first year off therapy with a subsequent risk of relapse in the remaining patients at a rate of 2% to 3% per year for the next 3 to 4 years [16].

Risk stratification of Acute Lymphoblastic Leukemia

Cases of acute lymphoid leukemia are usually first categorized by immunophenotyping and include the early B-cell, mature B-cell and T-cell lineages. Early B-cell lineage is the most common subgroup, and within this lineage, the following four risk groups with different outcomes have been identified based upon initial clinical and biological risk factors.

Low-risk — Children with favorable age, low WBC count and favorable cytogenetic changes, such as hyperdiploidy, trisomies of 4, 10, and 17 or the presence of the ETV6FUNX1 (formally TEL-AMIL) fusion protein, are in the low-risk group and have the best prognosis, with reported four to five year, event-free survival (EFS) rates approaching 90 percent .

Standard-risk — Patients with favorable age and low WBC count, but without favorable cytogenetic changes, are considered to have standard-risk ALL.

High-risk — Patients older than 10 years of age, or those with unfavorable cytogenetic changes, are considered to have high-risk ALL.

Very-high risk — Children in the very-high-risk group include those with cytogenetic markers of extreme hypodiploidy, t (9; 22) BCR/ABL translocation (Philadelphia chromosome), t (4; 11) MLL rearrangement, and/or failure to achieve remission at the end of induction therapy.

Support of risk stratification was illustrated in a retrospective review of 6238 children with ALL from the Children's Oncology Group. Risk stratification was based upon age, WBC count, sex, extramedullary disease, blast cytogenetics and ploidy, and early response to therapy [17, 18].

Prognosis Based on Risk Stratification[17, 18].

Risk Stratification	**4 year Event Free Survival**
Low risk	92 percent
Standard risk	82 percent
High risk	73 percent
Very high risk	46 percent

Treatment:

The single most important prognostic factor in ALL is the treatment. Without effective therapy the disease is fatal. The survival rates of children with ALL over the past 40 years have improved, because the clinical trials have immensely improved the therapy and outcomes.

Risk Group based Therapy [19]

Risk Stratification	**Recommended Therapy**
Low risk	Conventional anti-metabolite-based therapy
Standard risk	Intensified antimetabolite therapy
High risk	Intensive multi-agent therapy
Very high risk	Allogeneic hematopoietic cell transplantation in first remission

Generally the treatment includes the combination of chemotherapy and cranial radiation. Under some circumstances only chemotherapy is given based on the intensity of the disease.

Some of the treatment protocols used for ALL treatment in different cancer centers around the globe are Berlin, Frankfurt, Munich (BFM) 86, BFM 95, CCG – BFM standard therapy, Augmented BFM therapy etc [20, 21].

Treatment of ALL frequently involves high-dose Methotrexate administered before radiation therapy to the brain. Although different mechanisms have been postulated to explain the underlying neurological basis of neurocognitive

dysfunction, damage to cortical and subcortical white matter has received the most attention [8]. Iuvone et al. reported that children with ALL who had been treated with a combination of cranial radiotherapy [CRT] and intrathecal [IT] methotrexate evidenced brain calcifications on neuroimaging scans [22]. The number of doses of IT methotrexate was associated with these calcifications and with neurocognitive decline. No difference in neurocognitive functioning was noted between those treated with CRT at either 18 Gy or 24 Gy.

Although CRT has been strongly implicated in white matter changes, chemotherapy alone may have similar effects. Wilson et al. demonstrated white matter abnormalities in patients with ALL who were treated with chemotherapy that consisted of prednisone, vincristine, L-asparaginase, and intravenous methotrexate. However these white matter changes had resolved in most of these patients after treatment [23].

Radiation Therapy

When radiation is delivered to the brain, the effects are generally described as occurring in three stages: acute, sub acute (or early delayed), and late. The acute effects are generally associated with sudden neurological deterioration following radiation therapy but have also been associated with certain types of chemotherapy, including L-asparaginase and methotrexate [24]. During the subacute period (2 to 6 months after radiation therapy), the "somnolence syndrome" is often observed and is associated with fatigue or an exaggeration of the neurological signs. This is believed to be secondary to diffuse demyelization, but the clinical symptoms are generally transient. Finally, late

effects of CRT are characterized by various neurological deficits and are largely believed to be responsible for the gradual neurocognitive decline often observed in young children, possibly as a result of an imbalance in the development of grey and white matter[16].

Moore et al studied 33 long-term non–brain tumor cancer survivors treated with a variety of protocols: 11 with leukemia had received IT chemotherapy plus CRT; 9 with sarcoma, Hodgkin's disease, or Wilm's tumor had been treated without any CNS therapy; and 13 with leukemia or lymphoma had received only IT chemotherapy. The group receiving a combination of CNS therapies had significantly lower performance on neuropsychological tests and significantly slower reaction time compared to those treated without CRT. Compared to the survivors in the other groups, the combined-therapy participants also had significantly smaller amplitude and slower response of the P-300 (a brain-evoked potential associated with attention). Because one function of myelin (i.e., white matter) is to increase axonal conduction velocity, the results of this study suggest that the effect of CRT impeded neuronal transmission speed, resulting in a slowing and dis- organization of cognitive processing that was manifested in neurocognitive deficits [25].

Neurocognitive Outcome in Survivors of Leukemia

Despite a large literature on the effects of CRT on neurocognitive outcome in children with ALL, studies of the effects of chemotherapy in isolation are far less frequent [22]. Literatures on the effect of ALL treatment on neurocognition are varied and difficult to interpret in view of various methodological restrictions and

differences in study designs, patient characteristics, types of reference group and chemotherapeutic regimens [26]. There is paucity of longitudinal prospectively conducted studies on the combined effect of high dose methotrexate and 18 Gy presymptomatic prophylactic cranial radiotherapy on neurocognition. There is no data on the effect of High dose methotrexate and cranial radiotherapy in Indian children treated for Acute lymphoblastic leukemia.

Effect of Chemotherapy without CRT on neurocognition:

Brown et al reported on 48 patients with ALL who were treated with a 3-year course of systemic and IT chemotherapy that included cyclophosphamide, L-asparaginase, intravenous methotrexate, and IT chemo- therapy (methotrexate, cytosine arabinoside, and hydro- cortisone). Findings revealed that the participants had significantly poorer performance on tests of attention and memory as well as visual construction ability than did those who had recently been diagnosed. Deficits were particularly notable in computational arithmetic skills that were consistent with a learning disability[27].

Von der Weid et al. compared 132 ALL survivors treated with chemotherapy alone to 100 children with non-CNS tumors who did not receive chemotherapy on standardized neuropsychological measures. Intellectual abilities were within the normal range and were comparable between the groups, suggesting that chemotherapy alone did not have an additional adverse effect on neurocognitive functioning above the cancer experience itself [28]. Copeland et al. studied 99 long term survivors treated with either IT chemotherapy or no CNS therapy; no child had been treated with CRT. The sample was diverse in terms of

diagnoses: ALL, Hodgkin Lymphoma, Osteosarcoma, Ewing's sarcoma and others. Of the children in the study, 73% had a diagnosis of leukemia or lymphoma. Patients treated with IT chemotherapy received methotrexate, cytarabine, and hydrocortisone. After they had been diagnosed, researchers assessed the children four times between 5 and 11 years for neurocognitive side effects. Mean scores for the IT chemotherapy and the no-IT chemotherapy groups were within the average range, and there was no statistically significant difference between the two groups. There was, however, a significant group by time interaction, whereby the group receiving IT chemotherapy had deteriorating motor skills and those in the no-IT chemotherapy group improved. Copeland et al. concluded that chemotherapy has only a slight effect on neurocognitive status [29].

Effect of Gender on neurocognition:

Several studies have demonstrated an increased vulnerability of females to the neurocognitive morbidity associated with CNS treatment [30, 31, 32], although not all studies have supported this effect [33]. Von der Weid et al. reported that girls with ALL who were treated with chemotherapy but not CRT had significantly low verbal and nonverbal performance IQ scores [34]. Compared to boys, approximately three times as many females had an IQ lower than one standard deviation below average. Brown et al. Reported that girls, but not boys, who had been treated for ALL had scores on nonverbal tests that were below average [35].

Age at Time of Diagnosis and Therapy

Young age has been strongly implicated in poor neurocognitive outcomes following treatment for cancers that involve the CNS [36,37,38]. This makes sense given what is known about the development of the nervous system and, in particular, cortical and sub cortical white matter. Substituting or delaying the use of CRT in very young children may lessen the neurocognitive morbidity without compromising the medical outcome in infants with brain tumors[38,39]. Among children with brain tumors who were under 3 years of age when diagnosed, those who were treated without CRT had scores within the average range of intellectual functioning and academic achievement, but those who were treated with CRT had significant deficits in verbal and performance IQ, academic achievement, memory, visual–spatial skills, fine motor skills, and attention abilities [38].

In a study of 27 children diagnosed at less than 3 years of age with a cerebellar tumor, Copeland et al. concluded that neurocognitive outcome is generally positive when treatment includes only surgery and chemotherapy[37]. These results are in partial agreement with other studies demonstrating that chemotherapy regimens, at least those that do not include methotrexate, are less benign in terms of cognitive toxicity [40, 41]. Packer et al. reported that children with primary brain tumors who were treated without CRT experienced no significant decline in their intellectual abilities 2 years following treatment. Overall, those who were managed with CRT evidenced a 14-point decline in full-scale IQ, but for those under the age of 7 years, the decline was 25 IQ points [41].

Time since Treatment

Cross-sectional studies have provided data suggesting that neurocognitive status declines with increasing time since treatment with CRT [16]. In contrast, Williams et al. found no significant declines or differences in the neurocognitive performance of children with ALL who were treated with either IT methotrexate alone, 18 Gy CRT plus IT methotrexate, 24 Gy CRT plus IT methotrexate, or intensive systemic chemotherapy plus 24 Gy delayed CRT. Children were assessed only 1 year after diagnosis, leading the investigators to suggest that the effects of CNS therapies, including CRT, are delayed in their onset[42]. In another study employing a cross-sectional design, children with ALL who had received a 3-year course of chemotherapy were more impaired, especially on tasks involving right-hemisphere simultaneous processing, than were sibling controls or other children with ALL who had been recently diagnosed and whose treatment had only recently begun[35]. The relation- ship between age at the time of treatment and elapsed time since treatment may be domain specific. Dennis et al. reported an age effect on nonverbal abilities, but not verbal abilities, in children with medulloblastoma treated with CRT; younger age at treatment was associated with poorer nonverbal abilities. Interestingly, for these patients it was verbal abilities, not nonverbal abilities that declined with increasing time since treatment [43].

Effect of steroids on Neurocognition

Waber et al. conducted a comparative study to find out the cognitive sequelae of treatment for childhood ALL in a group of patients who received dexamethasone during the intensification and maintenance phases of therapy with those in a historical control group for whom antileukemia therapy was similar, except that the corticosteroid component of therapy was prednisone. Patients treated for ALL on Dana-Farber Cancer Institute protocols 87-01 (n = 44) and 91-01 (n = 23) were evaluated by standard cognitive and achievement tests. Corticosteroid therapy was delivered in five day pulses given every three weeks during intensification and continuation phases of therapy for a total of two years. The children treated on protocol 87-01 received prednisone at a dose of 40 $mg/m^2/d$ (standard risk, SR) or 120 $mg/ m^2/d$ (high risk, HR); those treated on protocol 91-01 received dexamethasone at a dose of 6 mg/m^2 per day (SR) or 18 mg/m^2 per day (HR). The results revealed that children treated on protocol 91-01 performed less well on cognitive testing. Subsample analysis indicated that cranial radiation therapy and methotrexate dose did not account for differences in cognitive outcomes. He concluded that dexamethasone therapy can increase risk for neurocognitive late effects in children treated for ALL and indicated further investigation of this question is warranted [44].

Effect of High dose methotrexate on neurognition

Effect of intravenous methotrexate dose and infusion rate on Neuropsychological function one year after diagnosis of ALL was tested by Carey et al. (2007). He compared 19 children treated with $1g/m^2$ of IV MTX over 24 hr

(Group 1) to 13 children treated with 2 g/m^2 of IVMTX over 4 hr (Group 2) on measures of working memory, nonverbal, and verbal skills shortly after diagnosis (Time 1) and 1 year later (Time 2). Results indicated a significant Group x Time interaction for a composite measure of working memory with Group 2 declining from Time 1 to Time 2. Group 2 performed significantly worse than Group 1 on a composite measure of nonverbal skills at both time points. Findings suggested that difficulties in working memory and nonverbal skills may be evident during the first year of treatment for ALL and that severity may be dependent on IV MTX dose and/or infusion rate [45].

Effect of Hyper fractionated Cranial Radiotherapy

Waber et al. evaluated the neuropsychologic sequelae after 8 years of survival in children with ALL treated in randomized clinical trial to test whether hyper fractioned (twice daily) cranial radiation therapy can reduce incidence and severity of late toxicities associated with 18 cGy of CRT. Between 1987 and 1995, 369 children treated on two consecutive Dana- Farber Cancer Institute Consortium Protocols for high- risk ALL were randomly assigned to conventionally fractionated CRT (CFX) or hyper fractionated CRT (HFX) to a total dose of 18 Gy. Neuro psychologic testing was completed for 125 of 287 children in continuous complete remission. Event free and overall survival as well as neuropsychologic function was compared for the two arms of the protocol. Results revealed that eight year event-free survival (± SE) was 80% ± 3% for children randomly assigned to CFX and 72% ± 3% for HFX (P=.06). Overall survival was 85% ± 3% for HFX (P=.06) CNS relapse occurred in 2.8% of patients receiving CFX and 2.7% receiving HFX.

Cognitive function for both groups was solidly in the average range, with no group differences in intelligence, academic achievement, visuospatial reasoning, or verbal learning. Children on the HFX arm exhibited a modest advantage for visual memory ($P<.05$). HFX provides no benefit in terms of cognitive late effects and may compromise antileukemic efficacy. He recommended that HFX should not be substituted for conventionally dosed CRT in children who require radiation therapy for treatment of acute lymphoblastic leukemia [46].

Methodological Issues

A number of methodological issues have been identified that make research complex regarding neurocognitive outcome of children treated for cancer[47]. These include difficulties conducting longitudi- nal studies, characteristic small sample sizes, missing data through attrition, and determining the optimal timing of the baseline evaluation.

Longitudinal Studies

For the purpose of describing the evolution of neurocognitive changes related to treatment, longitudinal designs are far superior to cross-sectional designs but are subject to certain biases, such as the selective attrition of participants due to progressive disease and death. Longitudinal studies, by definition, take more time to complete than do cross-sectional studies. However, cross-sectional studies may have a larger number of available patients to study but are limited to indirect implications regarding time since diagnosis and age of the child at the time of treatment. New therapies and monitoring techniques are rapidly

evolving so that by the time a longitudinal study is completed and published; newer therapies may have replaced the ones being studied. Because cancer in children is rare and because an individual medical center caring for patients with cancer has only a limited population from which to select participants, studies often have insufficient statistical power to detect significant main effects. This can be mitigated by research within the large multi-institutional clinical trials groups. The Children's Oncology Group is the largest of these collaborative groups and has an active program that studies the neurocognitive outcome of children treated with various treatment protocols for cancer. Many studies, however, have been plagued by low patient accrual and poor adherence with the demands of study participation and data collection. In one of the most successful studies within the cooperative groups (Children's Cancer Group 9892), only 66% of eligible patients had more than a single evaluation over a 4-year period, and data accrued were limited primarily to measures of intellectual functioning[47]. The Children's Oncology Group has recently adopted a core battery of standardized neurocognitive assessment measures in an attempt to increase accrual and compliance and to enable comparisons of outcomes across studies.

Variables Considered under Neurocognitive assessment:

As the study focuses on the effect of treatment on cognitive function, the variables considered under this broad term are described here in the following paragraphs.

Cognition

The term cognition refers to higher intellectual processes such as thought, memory, attention, and complex perceptual process. Each functional aspect of cognition comprises many discrete activities—such as color recognition or immediate memory for spoken words. Although each function constitutes a distinct class of behaviors, normally they work in close, interdependent concert. Generally speaking, within each class of cognitive functions, a division may be made between those functions that mediate verbal/symbolic information and those that deal with data that cannot be communicated in words or symbols, such as complex visual or sound patterns. These subclasses of functions differ from one another in their neuroanatomical organization and in their behavior expression while sharing other basic neuroanatomical and psychometric relationships within the functional system [47, 48, and 49].

Attention

Attention is the first step in the learning process. We cannot understand, learn or remember if we do not first attend to. Attention involves a number of processes including filtering out perceptions, balancing multiple perceptions and attaching emotional significance to these perceptions.

Active attention is a multidimensional cognitive process that includes the ability to select and focus on what is important at any given moment, the ability to consistently maintain mental effort while performing tasks that require mental energy and the ability to inhibit action or thought while previewing alternative actions or thoughts. In other words, it is a complex process that includes feeling alert

and aroused, selecting what we should be attending to, ignoring what we don't want to attend to, and maintaining our focus for the right amount of time. Attention allows us to plan or preview and monitor and regulate our thoughts and actions [50, 51].

Selective attention

The term selective attention refers to the fact that we usually focus our attention on one or a few tasks or events rather than on many. As attention researcher Pashler puts it, “At any given moment, (people’s) awareness encompasses only a tiny proportion of the stimuli impinging on their sensory systems” [52].

Vigilance:

Vigilance refers to a person’s ability to attend to a field of stimulation over a prolonged period, during which the person seeks to detect the appearance of a particular target stimulus of interest. When being vigilant, the individual watchfully waits to detect a signal stimulus that may appear at an unknown time. Typically, vigilance is needed in settings where a given stimulus occurs only rarely but requires immediate attention as soon as it does occur. The successful performance of any task involving attention, concentration or tracking requires sustained, focused attention. [47, 48, and 49].

Visuo spatial functioning:

Visuo spatial skill is an important component of cognitive function in which young children develop basic spatial understanding that forms the basis for geometry. One such basic understanding is spatial visualization. This is our ability to

orient ourselves in our surroundings and to manipulate images of objects mentally[50. 51].

Memory:

Memory is the means by which we retain and draw on our past experiences to use that information in the present. As a process, memory refers to the dynamic mechanism associated with storing, retaining and retrieving information about past experience. Severely impaired memory isolates patients from emotionally or practically meaningful contact with the world about them and deprives them of a sense of personal continuity, rendering them passive and helplessly dependent. Mildly to moderately impaired memory has a disorienting effect.

Visual memory is a part of memory preserving some characteristics of our senses pertaining to visual experience. Visual memory involves the ability to store and retrieve previously experienced visual sensations and perceptions when the stimuli that originally evoked them are no longer present. Various researchers have stated that as much as eighty percent of all learning takes place through the eye with visual memory existing as a crucial aspect of learning. Children who have not developed their visual memory skills cannot readily reproduce a sequence of visual stimuli. These students fail to develop a good sight vocabulary and frequently experience serious writing and spelling difficulties [53, 54].

Thinking:

Thinking may be defined as any mental operation that relates two or more bits of information explicitly (as in making an arithmetic computation) or implicitly (as in judging that this is bad, i.e., relative to that). A host of complete cognitive

functions is subsumed under the rubric of thinking, such as computation, reasoning and judgment, concept formation, abstraction and generalizing, ordering, organizing planning, and problem solving [55].

Ideation fluency:

Ideation fluency also called as verbal fluency is the expressive ability to produce linguistic output. When we deal specifically with spoken communication, we can refer to vocal comprehension or fluency. For example, people may be able to understand languages well but not produce it well or vice versa.

It is well understood that the cognitive process is one of the important aspects in the process of human development. During the normal course of development when there is a disturbance in the cognitive function, it affects the child immensely in the area of intellectual and academic prosperity and almost every other aspect of its life. In this context, many researchers have indicated that cognitive function is affected due to the treatment in ALL.

Cognitive rehabilitation or retraining

After identifying the cognitive dysfunction in ALL patients treated with CRT and High dose methotrexate, it is very important to rehabilitate them. The purpose of cognitive retraining is the reduction of cognitive problems associated with treatment related brain injury and thereby improve their overall level of functioning and quality of life. The overall purpose of the therapy is to decrease the everyday problems faced by individual with cognitive difficulties.

Cognitive rehabilitation is defined as a systematic, functionally oriented service of therapeutic activities that is based on assessment and understanding of the patient's brain-behavioral deficits. Various techniques used for cognitive rehabilitations are as follows

.**Techniques:**

1. Reinforcing, strengthening, or reestablishing previously learned patterns of behavior.

2. Establishing new patterns of cognitive activity through compensatory cognitive mechanisms for impaired neurological systems

3. Establishing new patterns of activity through external compensatory mechanisms such environmental restructuring and support

4. Enabling persons to adapt to their cognitive disability

Cognitive rehabilitation may be directed toward many areas of cognition, including (but not necessarily limited to) attention, concentration, perception, memory, comprehension, communication, reasoning, problem solving, judgment, initiation, planning, self-monitoring, and awareness. An individualized program which uses multisensory method to compensate for weaker abilities is also available. Exceptional cases not responding to these treatments may require special schools for training in scholastic skills. Regardless of the specific approach or area of intervention, cognitive rehabilitation services should be directed at achieving changes that improve each person's function in areas that are relevant to their everyday lives [56, 57, and 58].

PATIENTS AND METHODS

Inclusion Criteria

- All patients diagnosed with acute lymphoblastic leukemia in the age group of 06 to 25 years.
- Patients started on BFM 86 treatment protocol & received both cranial radiotherapy and High dose methotrexate as per the protocol were included after taking informed consent.

Exclusion Criteria

- Patients with past history of any psychiatric illness or neurological disorders or developmental delay.
- Patients diagnosed to have CNS involvement upfront by CSF analysis or MRI Brain.
- All Patients with Acute Lymphoblastic Leukemia who did not achieve remission or relapsed while on treatment before the third assessment.

Study Period – Mar 2008 to Feb 2009

Materials and Methods;

Patients diagnosed with Acute Lymphoblastic Leukemia (ALL) were inducted in to the study for the initial baseline assessment immediately after stabilization of general condition.

The first post treatment assessment was undertaken after the completion of reinduction phase before giving cranial radiotherapy.

The second post treatment assessment was undertaken within one year of initial baseline assessment.

Each assessment was carried out by a team of two persons comprising of an oncologist and a psychologist.

General linear model: repeated measure analysis of variance was used to find out the difference between baseline and two post treatment assessments on cognitive function. The obtained data was analyzed using SPSS version 13.

Table: shows the assessment of cognitive function and the treatment regimen.

Sl.No.	Assessment points	Treatment regimen	Time Frame
1.	Baseline assessment	At diagnosis	D15 to D30 of Induction I
2. .	First-post treatment assessment.	After reinduction I & before cranial Radiotherapy.	After D29 of Reinduction I [D150 – 180]
3.	Second post treatment assessment	After a minimum of 1 year of first assessment	After 5th monthly maintenance [D390 – 420]

BFM 86 Protocol used for the current study: Schedule

Induction:	**Dose**	**day**
Tab Prednisolone	60mg/m^2	1 - 28
Vincristine	1.5 mg/m^2	8, 15, 22, 29.
L- Asparaginase	10000iu/m^2,	19,22,25,28
Daunorubicin	40 mg/m^2 .	8, 15, 22, 29
Methotrexate:	12 mg Intrathecal	1, 45, 59.
6 – mercaptopurine	60 mg/m^2	43 – 70
Inj Cyclophosphamide	1000 mg/m^2 IV	43, 71.
Inj Cytarabine	75 mg/m^2 IV	45-48, 52-55, 59-62, 66-69.

Consolidation	**Dose**	**day**
High Dose Methotrexate:	5g/m^2 (24hr inf)	8,22,36,50
6 – mercaptopurine	25 mg/m^2	D 1- 56
Methotrexate:	12 mg Intrathecal	8,22,36,50.

Reinduction: I	**Dose**	**day**
Dexa	10 mg/m^2	1-21
Vincristine	1.5 mg/m^2	8, 15, 22, 29.
Adriamycin	30 mg/m^2 .	8, 15, 22, 29
Methotrexate:	12 mg Intrathecal	1, 45, 59.
Cranial Radiotherapy – 18 Gy **Reinduction II**		
Thioguanine	60 mg/m^2 Oral	36 - 49
Inj Cyclophosphamide	1000 mg/m^2 IV	36
Inj Cytarabine	75mg/m^2	38-41, 45-48
Methotrexate:	12 mg Intrathecal	38, 45

MAINTENANCE

Methotrexate:	20mg/m2 oral
6 mercaptopurine	50mg|m2 oral

Variables measured in age group 6 to 15 years are

- Attention
- Vigilance
- Visuo Spatial Functioning.
- Learning and Memory
- Ideation Fluency
- Problem solving capacity.
- Intelligence quotient

Tools used

I. ATTENTION & MEMORY

- Digit span Test (WISC) [59]
- Coding (WISC) [59]

II. VIGILANCE

- Vigilance Test. (Strub and Black, 1995) [60]

III. VISUO SPATIAL FUNCTIONING

- Object Assembly, (WISC) [59]
- Block Design, (WISC) [59]

IV. Logical memory

- Ideation Fluency Test. (Mukundan and Rao, 2005) [59]

V PROBLEM SOLVING ABILITY

- Maze (WISC) [59]

VI INTELLIGENCE

- Intelligence Quotient (WISC) [59]

Variables measured in age group 16 to 25 years are

- Attention
- Visuo Spatial Functioning.
- Learning and Memory
- Intelligence quotient

Tools used

I. ATTENTION & MEMORY

- Digit span Test (Wechsler, 1997)[62]
- Digit Symbol Substitution Test. (Wechsler, 1997) [62]

II. VISUO SPATIAL FUNCTIONING

- Object Assembly, (Wechsler, 1997) [62]
- Block Design, (Wechsler, 1997) [62]

III INTELLIGENCE

- Intelligence Quotient (Wechsler, 1997) [62]

- WISC [Wechsler's Intelligence scale for Children, Dr. A.J.Malin's Indian Adaptation] assesses individually each domain and the performance in each domain is measured as raw score. Later this raw score is converted in to IQ using tables. Same Raw score may have different IQ based on the age of the patient. Average of the entire IQ is taken to calculate the total performance IQ of each child.

- WAIS - Wechsler's Adult Intelligence scale assesses individually each domain and performance in each domain is measured as raw score. Later this raw score is converted to scaled scores with tables. Sum of all the scaled scores can be converted into performance IQ.

RESULTS

Although a total of 60 acute lymphoblast leukemia patients underwent the initial baseline assessment, only 49 patients completed all three assessments and were analyzed.

Table 1

Age	Number	Mean age(Y)
6 – 15 years	24	10.8
16 – 25 years	25	19.92

Fig 1

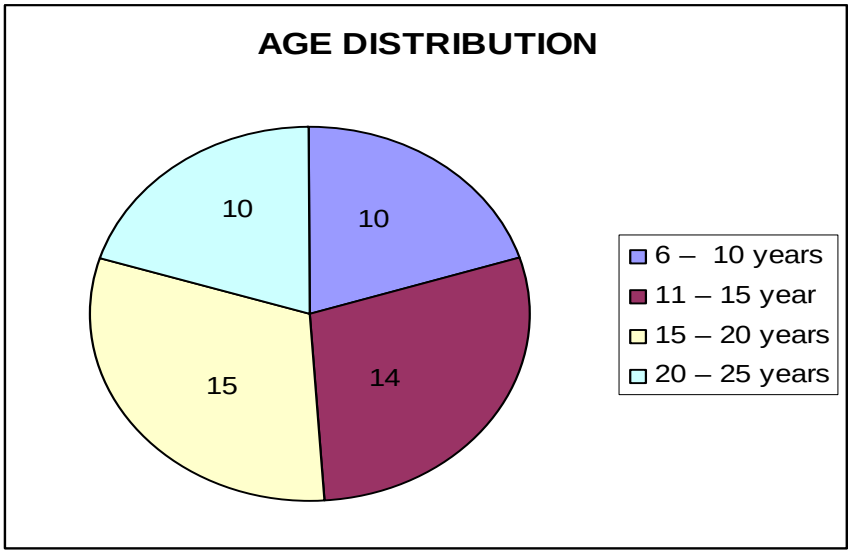
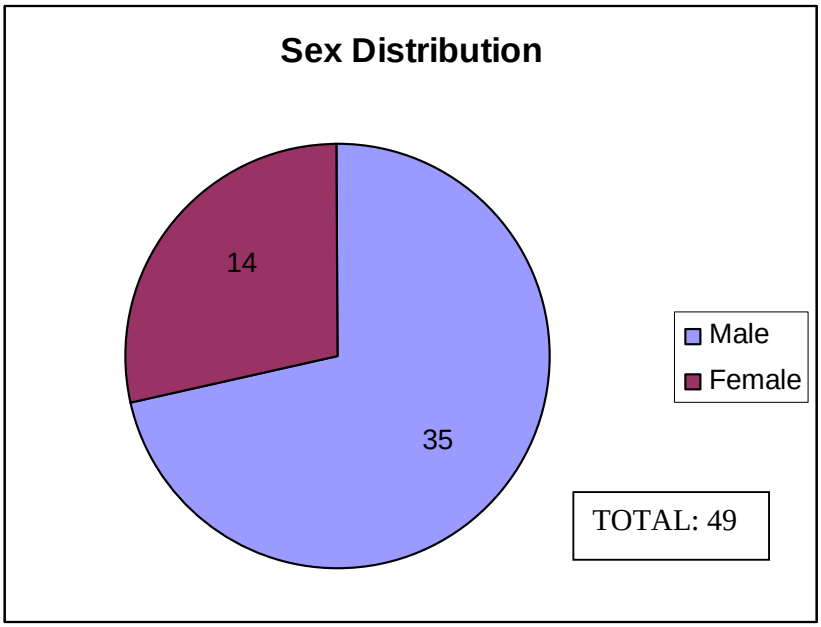


Fig 2



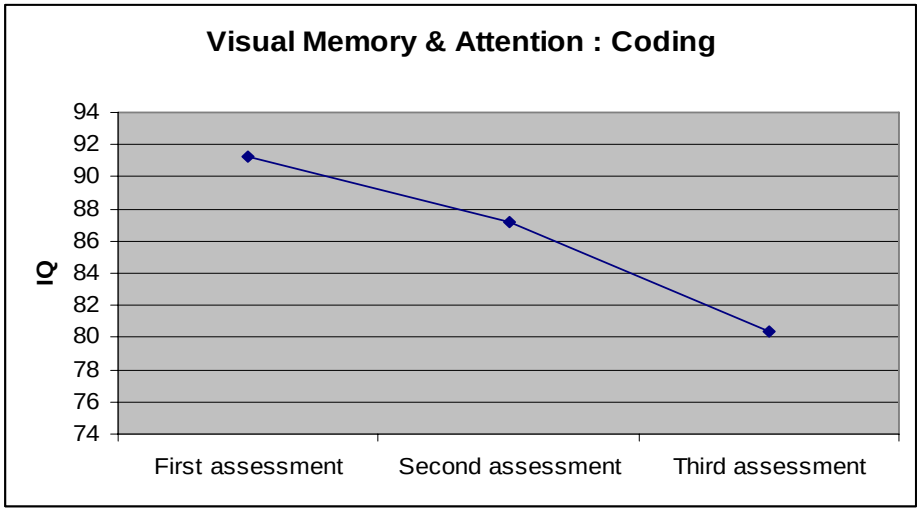
AGE GROUP: 6 – 15 years (n = 24)

Results of Test of Attention: - Coding

Table 2

Coding	Baseline Assessment	Second Assessment	Third Assessment	Significance
Mean Raw Score	30.38	28.33	29.75	0.652 **NS**
Mean IQ	91.21	87.21	80.33	0.05 **Sig**

Fig 3



- **Coding is a test of Visual memory and Attention among children.**

Digit span test

Table 3

MEAN VALUE	Baseline Assessment	Second Assessment	Third assessment	Significance
Digit Forward	4.75	4.75	4.13	0.08 **NS**
Digit Backward	3.71	3.5	2.96	0.09 **NS**
Digit Span: Total	8.13	8.17	7.08	0.1 **NS**

- **Digit span is a test of level of Verbal Attention and memory**

VIGILANCE

Table 4

MEAN VALUE	Baseline Assessment	Second Assessment	Third Assessment	Significance P Value
Omission	2.58	2.25	3.5	0.1 **NS**
Commission	2.00	2.17	3.00	0.1 **NS**

- **Vigilance Test measures the level of ability to sustain and focussed attention**

VISUO SPATIAL FUNCTIONING

Object Assembly:

Table 5

Object Assembly	Baseline Assessment	Second Assessment	Third Assessment	Significance
Mean Raw Score	13.42	15.04	13.33	0.3 **NS**
Mean IQ	85.92	90.79	79.92	0.1 **NS**

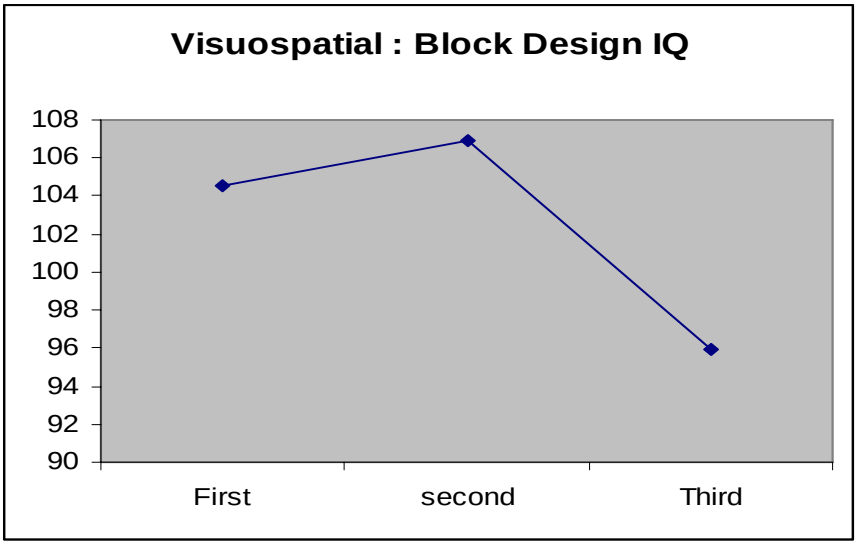
*** Object Assembly test the level of visual spatial ability among children.**

Block Design

Table 6

Block Design	Baseline Assessment	Second Assessment	Third Assessment	Significance
Mean Raw Score	19.67	21.5	18.04	0.4 **NS**
Mean IQ	104.54	106.96	95.96	0.049 **Sig**

Fig 4



Block Design is a test of visuo spatial and motor integration skills among children

Logical memory : Ideation Fluency Test

Table: 7

Ideation Fluency Test	Baseline Assessment	Second Assessment	Third Assessment	Significance
Circle (Mean)	5.31	5.90	4.72	0.2 **NS**
Wood (mean)	6.59	7.03	5.34	0.09 **NS**

- **Ideation and fluency assessment test the level of logical memory among children**

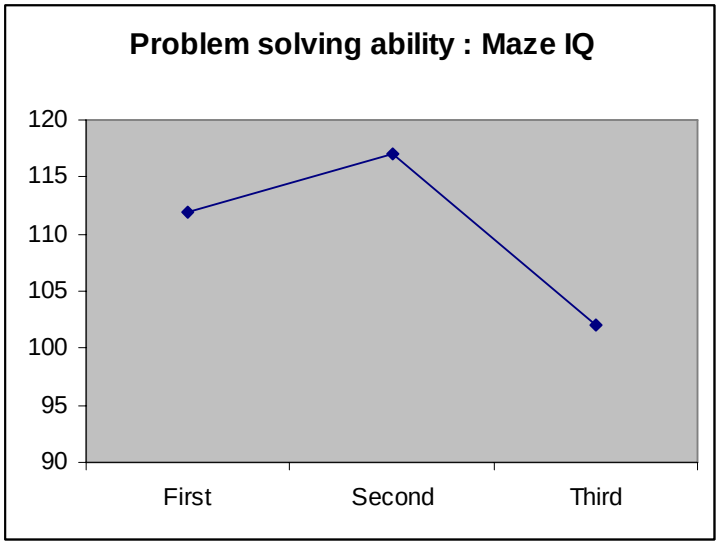
PROBLEM SOLVING ABILITY

Table 8

Maze

Maze	Baseline Assessment	Second Assessment	Third Assessment	Significance
Raw Score (mean)	16.13	17.38	15.08	0.1 **NS**
Mean IQ	112	117.38	102.58	0.002 **Sig**

Fig 5



*** Maze testing measures the level of problem solving capacity among children.**

Arithmetic Skill

Table 9

Arithmetic Skill	Baseline Assessment	Second Assessment	Third Assessment	Significance
Raw Score (mean)	9.72	9.55	9.14	0.6 **NS**
Mean IQ	98.62	97.28	91.34	0.1 **NS**

Total Performance:

Table: 10

Performance	Baseline Assessment	Second Assessment	Third Assessment	Significance
Total Raw Score	93.88	96.58	86.58	0.3 **NS**
Mean IQ	100.8	103.3	92.4	0.000 **Sig**

- **P < 0.05 considered Significant (sig)**
- **NS – Not Significant**

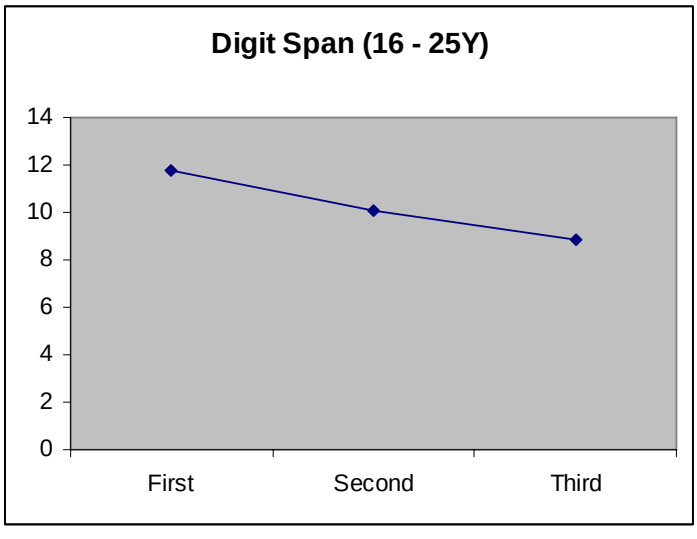
Adolescence and Young Adults Assessment: 16 – 25 years (n = 25)

ATTENTION & MEMORY

Digit Span: Table 11

MEAN VALUE	Baseline Assessment	Second Assessment	Third assessment	Significance
Digit Forward	5.84	5.80	5.20	0.02 **Sig**
Digit Backward	4.24	4.24	3.64	0.03 **Sig**
Digit Span: Total	11.88	10.04	8.84	0.04 **Sig**

Fig 6



*** Digit span is a measure of Verbal Attention and memory.**

Digit Symbol: Mean Raw Score

Table 12

Baseline Assessment	Second Assessment	Third Assessment	Significance
42.68	44.32	43.76	0.7 **NS**

Digit symbol measures the level of Visio motor, Attention and memory.

VISUO SPATIAL FUNCTIONING

Object Assembly

Mean Raw Score – Table 13

Baseline Assessment	Second Assessment	Third Assessment	Significance
18.24	19.76	18.40	0.5 **NS**

*** Object Assembly test the level of visual spatial ability.**

Block design: Mean Raw Score

Table 14

Baseline Assessment	Second Assessment	Third Assessment	Significance
24.44	25.72	24.64	0.5 **NS**

*** Block Design is a test of visuo spatial and motor integration skills.**

INTELLIGENCE QUOTIENT

Total Average IQ (mean) - Table 15

Baseline Assessment	Second Assessment	Third Assessment	Significance
98.32	98.84	98.16	0.9 **NS**

Note : P < 0.05 considered significant (sig)

NS – Not Significant

Effect of Age on Neurocognition:

Object assembly: WISC (IQ)

Age comparison (mean)

Table 16

AGE (years)	Baseline Assessment	Second Assessment	Third Assessment	Significance
6 – 10 (n=10)	106.6	109.4	84.5	0.01[Sig]
11 – 15 (n=14)	71.14	77.5	76.64	0.40[NS]

The table 29 shows that there is a significant difference among the baseline and two post treatment assessments on object assembly in the age group 6 to 10 years. No similar decline noticed in the age group 11 to 15 year age group.

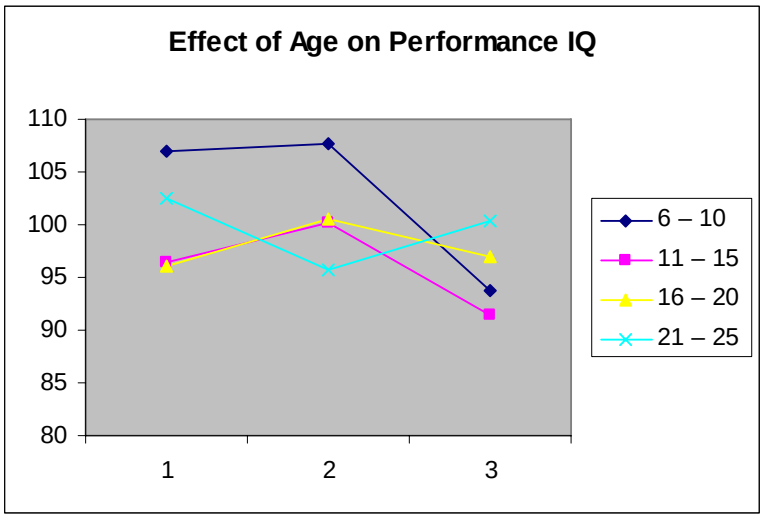
Effect of Age on Total IQ (mean)

Table 17

AGE (Years)	Baseline Assessment	Second Assessment	Third Assessment	Significance
6 – 10 (n = 10)	106.9	107.7	93.82	0.000 **[sig]**
11 – 15 (n=14)	96.5	100.25	91.48	0.006**[sig]**
16 – 20 (n = 15)	96.00	100.56	96.94	0.397**[NS]**
21 – 25 (n= 10)	102.44	95.78	100.33	0.786**[NS]**

The table 28 shows that there is a significant difference among the baseline and two post treatment assessments on Performance intelligent Quotient assessment in the age group 6 to 15 years. No similar decline noticed in the age group 16 to 25 year age group.

Fig 7



Effect of sex on Neurocognition:

Table 18

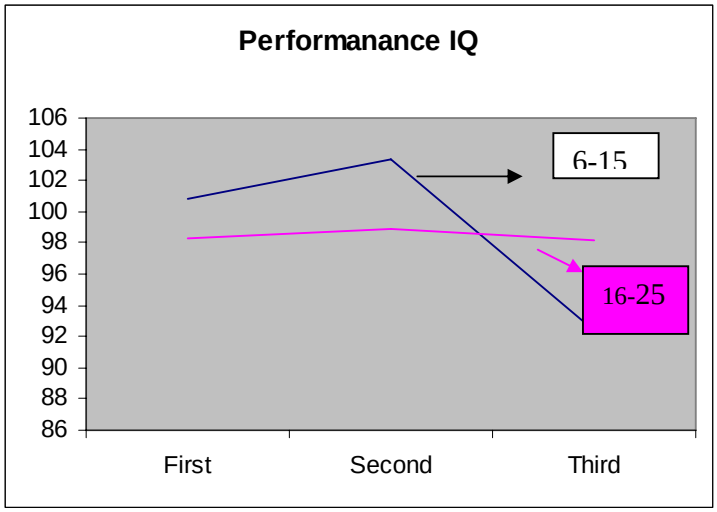
Total Average IQ (mean)

	Baseline Assessment	Second Assessment	Third Assessment	Significance
Age Group : 6 – 15 years				
Male (n = 15)	99.32	102.7	92.8	0.001
Female (n = 9)	103.96	105	95.18	0.025
Age group : 16 – 25 years				
Male (n = 20)	99.32	97.42	98	NS
Female(N = 5)	95.6	103.6	97.6	NS

Table 31 shows a decline in the performance IQ in the age group 6 to 15 years irrespective of the sex and no similar decline in the age group of 16 to 25 years in either sex.

Time since Treatment on Neurocognition:

Fig 8



- **NS – Not Significant**

DISCUSSION

Literatures on the effect of ALL treatment on neurocognition are varied and difficult to interpret in view of various methodological restrictions and differences in study designs, patient characteristics, types of reference group and chemotherapeutic regimens [26]. In our study the last neurocognitive assessment was done 1 year post diagnosis which may be early, since most of the radiotherapy related decline occurs late. This is in contrast to the chemotherapy related decline in cognition which occurs early and may be noticed as early as one year post diagnosis. There is paucity of longitudinal prospectively conducted studies on the combined effect of high dose methotrexate and 18Gy presymptomatic prophylactic cranial radiotherapy on neurocognition. There is no Indian data on the combined effect of high dose methotrexate and CRT on neurocognition

ATTENTION & MEMORY

Visual attention and memory was assessed in the age group 6 to 15 years by coding test and in the age group 16 to 25 years with digit symbol test. The table 2 & Fig.3 shows that there is a significant decline in the level of Visual memory, processing speed and Attention among children with Acute Lymphoblastic Leukemia on BFM 86 protocol treatment in the age group 6 years to 15 years. Vigilance, assessed with Strub and Black test did not show decline between assessments in the age group less than 15 years (table 4).

There was no significant decline in attention in ALL patients older than 15 years (table 11) as measured by digit symbol test.

Thus decline in the coding IQ is suggestive of loss of visual memory, focused attention and possessing speed. Similar impact was not observed in our adolescent and young adult population. There was no decline in the verbal attention after chemotherapy and cranial radiation in the current study.

Brown et al reported on 48 patients with ALL who were treated with a 3-year course of systemic and IT chemotherapy had significantly poorer performance on tests of attention and memory as well as visual construction ability. Several reports have indicated that children treated with CRT tend to show greater impairments in selective (focused) attention and attention shifting [27, 63, 64, 65, and 66]. Numerous studies have reported that the effect of chemotherapy and cranial radiotherapy is less in adolescence and young adults [67, 68, 69, and 70]. In our study there was no significant decline in attention and memory in age group of 16 to 25 years.

Visuospatial Functioning

Visuospatial functioning across the age group (6 to 25 years) in our study was tested with object assembly and block design testing.

In the age group 6 to 15 years results demonstrated significant decline in the visuospatial and motor integration skills after chemotherapy and cranial radiation as measured by the decline in the Block design IQ post treatment (fig 4, table 6). No decline in spatial ability & reasoning was noticed as measured by the object assembly testing (Table 5). Espy et al, Hill et al and Ciesielski et al reported similar deficit in patients receiving chemotherapy alone[71, 72, 73].

In the present study results, the deterioration of visuo spatial functioning was observed only in the age group less than 15 years. Both the test did not show any significant decline between the baseline assessment and two post treatment assessment in older patients (16 to 25 years). This may be explained by the differential sensitivity of the young patients to neurotoxicity [67, 68, 69, and 70]

Memory

Memory has many components. In our study Verbal memory was tested by digit span in both the age groups and Logical and long term memory was tested by Ideation and Fluency only in the less than 15 years age group. Visual memory which was tested by coding in less than 15 years and by the digit symbol in older patient has been discussed above under the title of attention (Table 2, 12 & Fig 3)

There was no significant decline in the level of Verbal Attention and memory among children with Acute Lymphoblastic Leukemia as measured by Digit span in the age group less than 15 years (table 3). There was no decline in the logical and long term memory as tested by ideation and fluency in the age group 6 to 15 years (Table 7). Verbal memory in the age group more than 15 years as tested by digit span showed a significant decline post treatment (Table 11 & Fig.6).

In our study visual memory was predominantly affected in less than 15 years whereas the verbal and logical memory was spared. Giralt et al. and Hill et al. have also reported similar sparing of verbal memory in children treated for ALL [73, 74].

In age group of more than 15 years verbal learning is predominantly affected with relative sparing of visual memory. Waber et al. & Precourt et al. reported

similar deficit in verbal learning in ALL girls treated with the combination of Intrathecal Chemotherapy (ITC) and CRT [75, 76].

Problem solving Ability

Problem solving ability was tested using Maze IQ assessment and arithmetic testing in the age group less than 15 years.

Maze testing assesses the problem solving capacity and involves visual processing, motor speed and integration. In our study there was a significant drop in maze IQ post treatment (Table 8, Fig 5).

Espy et al reported similar decline in visual motor integration skills in ALL patients treated with prophylactic CNS chemotherapy, intrathecal and systemic treatment at four years post diagnosis [71]. Schatz et al also reported significant delay in visiomotor processing speed in long-term survivors of childhood ALL [77].

In our study there was no drop in arithmetic IQ post treatment (Table 9). This is contrary to most of the studies which shows significant decline in arithmetic IQ post treatment [35, 64, and 78]. This may be due to the fact that most of the post cranial radiotherapy related decline cognition occurs late and assessment at one year Post diagnosis is early.

Effect of Age on IQ

There was a significant decline in the performance IQ post treatment in less than 15 years of age (Table 10 & 17, Fig 7). But the decline in Performance IQ post treatment in the age group more than 15 years was not statistically significant (table 15 & 17). Among the age group of 6 to 15 years, Visual attention, processing and motor integration is more affected in less than 10 years in comparison to more than

10 years (Table 16). Most of the reports has suggested that age at treatment is a proxy variable for underlying neurodevelopment maturity. While development of cortical gray matter peaks at approximately 4 years of age, cortical white matter volume continues to rise until about 20 years of age. Therefore, those who are younger at the time of radiation treatment generally have less fully developed white matter. However, since both younger and older patients have been shown to lose white matter volume at similar rates, the younger irradiated patients continue to display reduced total white matter volume following radiation treatment. These deficits in white matter volume among younger patients have also been associated with increased intellectual morbidity [67, 68, 69, and 70].

Effect of Sex on IQ:

The fall in the performance IQ post treatment was significant at the level of p value less the 0.01 in males and 0.05 in females (Table 18). There was no statistically significant decline in the performance IQ of either sex in the age group more than 15 years. Except one study [33], most of the literature evidence suggest that female sex is more prone for neurocognitive side effects than males due to gender difference in brain maturation [30, 32, and 32]. Similar observation was not observed in our study may be due to small sample size and also due to inadequate number of female patients.

Time since Treatment on Neurocognition:

There was a non significant increase in performance in most of the domains and performance IQ in the age group 6 to 15 years. This may be explained by the practice

effect. Since the second assessment was done before cranial irradiation, most of our patients underwent second assessment in less than 6 months of baseline assessment. This would have led to the better performance in the second assessment in comparison to the baseline. In contrast there was significant decline in performance IQ at 1 year of diagnosis in the age group 6 to 15 years. No such trend was seen in older patients (16 to 25 years) [Fig 8]. Most of the studies have suggested that the effects of CRT on the brain and on neurocognitive abilities are progressive, yet they seem to be delayed in onset [79 - 84]. Williams et al. found no significant decline or differences in the neurocognitive performance of children with ALL who were treated with either IT methotrexate alone, 18 Gy CRT plus IT methotrexate, 24Gy CRT plus IT methotrexate or intensive systemic chemotherapy plus 24Gy delayed CRT. Children were assessed only 1 year after diagnosis, leading the investigators to suggest that the effects of CNS therapies, including CRT, are delayed in their onset. Anna Abraham et al in a study at Kidwai Memorial institute of oncology, Bangalore has reported drop in intelligence quotient as early as 10 months median time after diagnosis in patients of ALL treated with MCP 841 protocol treatment [85]. Another Indian study by Jain et al from AIIMS, New Delhi has also reported low intelligent quotient post CRT treatment in cases of ALL patients in comparison with matched controls [86]. Although most of the studies has suggested that effect of cranial radiotherapy on neurocognition may be delayed and progressisive, the studies on the effect of the high dose methotrexate are varied. Carey et al and Paul Krappmann et al reported drop in intelligence quotient as early as at the end of one year of initiating treatment [45, 87]. While other studies show that, children receiving chemotherapy alone

perform similar to controls, suggesting that such treatment is not associated with intellectual sequelae [88-91]. But the problem with most of these studies is that, they are cross sectional studies without baseline assessment and it is difficult to come to a conclusion regarding the effect of chemotherapy alone on neurocognition.

Our study is unique in that, it is a prospective longitudinal study attempting to identify cognitive impairment as early as one year after diagnosis in ALL patients treated with BFM 86 protocol treatment in India. Identifying cognitive dysfunction may help us to institute rehabilitation early and thereby improve their overall level of functioning and quality of life. Parental counseling and informing school teachers regarding the cognitive dysfunction also plays an essential part of cognitive rehabilitation.

In our study, although there was a decline in IQ in less than 15 year of age, the mean IQ was within the average range (90-109). Long term follow-up of these patients will reveal whether this cognitive dysfunction is constant or deteriorating or improving. Apart from the performance IQ, we also have identified certain domains which are predominantly affected by BFM 86 protocol treatment. These patients will benefit by early educational intervention directed to overcome their difficulties. An individualized program which uses multisensory method to compensate for weaker abilities is also available. Exceptional cases not responding to these treatments may require special schools for training in scholastic skills [56, 57 and 58].

Conclusions

1. Visual memory, focused attention, visuospatial ability, motor integration and processing speed are the predominant components of neurocognition affected in ALL patients in the age group 5 to 15 years treated with BFM 86 protocol treatment at the end of one year after diagnosis
2. Verbal Attention and memory is the predominant component of neurocognition affected in ALL patients of the age group 16 to 25 years treated with BFM 86 protocol treatment at the end of one year after diagnosis
3. Impact of therapy on performance Intelligence quotient is noticed only in younger patients (5 to 15 years) treated with BFM 86 protocol treatment. No similar impact seen in older age group (16 to 25 years).
4. No significant difference noticed in the effect of treatment on neurocognition based on Sex of ALL patients in our study group.
5. The present study strongly implicates that effect of combined cranial radiotherapy and high dose methotrexate on neurocognition occurs early especially in patients less than 15 years of age and early intervention on cognitive rehabilitation is vital for these patients.

Limitations

1. Present study limits only to the immediate effect, the long term effect was not studied.
2. The present study did not try to find the effect of chemotherapy and radiation on neurocognition individually.
3. Current results are restricted to the age group of 6 to 25 years of age group; hence it cannot be generalized to other age groups.
4. Verbal Intelligent quotient could not be assessed due to the unavailability of assessment tools in local language.

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